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December 8, 2003
Date

Michael R. Krawzenek

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Polonsky *et al.*

Serial No.: 09/768,877

Filed: January 23, 2001

For: METHODS OF TREATMENT OF TYPE 2 DIABETES

Group Art Unit: 1652

Examiner: Ramirez, D.M.

Atty. Dkt. No.: ARCD:307USD1

APPEAL BRIEF

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APPEAL BRIEF

MS Appeal Briefs
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Appeal Brief is filed in response to the Final Office Action mailed on March 26, 2003. The three-month date for submission of this Brief is September 8, 2003, by virtue of the date, July 7, 2003, stamped on the return postcard filed with the Notice of Appeal on June 25, 2003 and the fact that September 7, 2003 is a Sunday.

A request for a three-month extension of time to respond is included herewith along with the required fee. This three-month extension will bring the due date to December 8, 2003, which is within the statutory period. Should such request or fee be deficient or absent, consider this paragraph such a request and authorization to withdraw the appropriate fee under 37 C.F.R. §§ 1.16 to 1.21 from Fulbright & Jaworski Deposit Account No. 50-1212/ARCD:307USD1.

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I. STATEMENT OF INTEREST

The real parties in interest are the assignees, Arch Development Corporation and Board of Regents, The University of Texas System.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

III. STATUS OF THE CLAIMS

Claims 1-48 were originally filed. In the Supplementary Preliminary Amendment dated December 20, 2001, claims 1-17 and 22-48 were cancelled and claims 49-113 were added. Due to a restriction Requirement dated January 10, 2002, Appellants elected without traverse to prosecute Group 1, claims 18-21 and 49-64 drawn to a method of screening for a modulator of calpain function in a Response to the Restriction Requirement filed April 8, 2002. Claims 18-21 and 49-64 were pending prior to the Office Action dated October 16, 2002. Claim 114 was added in the response to the Office Action dated January 16, 2003. Therefore, the claims pending for the purpose of the present Appeal are claims 18-21, 49-64 and 114.

Appellants have submitted, concurrently with the filing of this Appeal Brief, an Amendment Under 37 C.F.R. §1.116. This Amendment is submitted to reduce the number of issues for appeal by resolving rejections under 35 U.S.C. §112, second paragraph. If this Amendment is entered, then the claims on appeal are the claims as set forth in Appendix A. If this Amendment is not entered, then the claims on appeal are the claims as set forth in Appendix B.

IV. STATUS OF THE AMENDMENTS

Appellants have submitted, concurrently with the filing of this Appeal Brief, an Amendment Under 37 C.F.R. §1.116. This Amendment is submitted to reduce the number of issues for appeal by resolving rejections under 35 U.S.C. §112, second paragraph.

V. SUMMARY OF THE INVENTION

The present invention relates to methods of screening for a modulator of calpain 10. Embodiments of the invention include methods of screening for a modulator of calpain 10 function comprising obtaining a calpain 10 polypeptide; determining a standard activity profile of the calpain 10 polypeptide; contacting the calpain 10 polypeptide with a putative modulator; and assaying for a change in the standard activity profile. Specification at least on page 7, line 11-16.

In certain embodiments, the calpain 10 polypeptide comprises the amino acid sequence of SEQ ID NO:2. The calpain 10 polypeptide may comprise amino acids 1 to 47 of SEQ ID NO:2. Specification at least on page 29, lines 19-26; in FIGs 1 and 5, and SEQ ID NO:2.

In certain embodiments, obtaining the calpain 10 polypeptide can comprise expressing the polypeptide in a host cell. The calpain 10 polypeptide can be isolated away from the host cell prior to contacting the calpain 10 polypeptide with the putative modulator. Specification at least on page 7, line 20-23 and pages 62-70.

In certain aspects, the standard activity profile of the calpain 10 polypeptide is determined by measuring the binding of the calpain 10 polypeptide to a synthetic substrate. The synthetic substrate may be Suc-Leu-Tyr-amidomethylcoumarin (AMC). Specification at least on page 7, line 20-23.

In particular embodiments, a method of screening for a modulator of calpain 10 function comprises obtaining an calpain 10 polypeptide; contacting the calpain 10 polypeptide with a putative modulator; and assaying for modulation of calpain 10 function by the putative modulator. Specification at least on page 7, line 11-16.

The calpain 10 polypeptide may comprise the amino acid sequence of SEQ ID NO: 2. In certain embodiments, the calpain 10 polypeptide has a sequence comprising amino acid 1 to 47 of SEQ ID NO:2. Specification at least on page 29, lines 19-26; in FIGs 1 and 5, and SEQ ID NO:2

In certain aspects, a method may comprise determining a standard activity profile of the calpain 10 polypeptide. The standard activity profile of the calpain 10 polypeptide may be determined by measuring the binding of the calpain 10 polypeptide to a synthetic substrate. The synthetic substrate can be Suc-Leu-Tyr-amidomethylcoumarin (AMC). Specification at least on page 7, line 20 to 23.

In particular embodiments, assaying for modulation of calpain 10 function comprises assaying for a change in the standard activity profile. Specification on page 7, line 11-16.

In other aspects, obtaining the calpain 10 polypeptide comprises expressing the polypeptide in a host cell. Specification at least on page 7, line 20 to 23 and pages 62-70.

In particular aspects, the calpain 10 polypeptide is isolated away from the host cell prior to contacting the calpain polypeptide with the putative modulator. Specification at least on pages 62-70.

In other aspects, obtaining the calpain 10 polypeptide comprises obtaining a cell containing the polypeptide. The cell can be a pancreatic cell, a muscle cell, an adipose cell, or a liver cell. In particular embodiments, the cell is a pancreatic cell. The pancreatic cell can be an

isolated pancreatic islet. The cell can be a β-cell. Specification at least on page 32, lines 1 to 5; pages 62-70; and pages 163 to 164.

VI. ISSUES ON APPEAL

A. Issues on Appeal, if the Amendment Filed Concurrently Herewith is Entered.

If the Amendment filed concurrently herewith is entered, then the claims on appeal with be the claims set forth in Appendix A, and the four issues on appeal will be as follows:

Issues under 35 U.S.C. 112, second paragraph:

1. Are claims 18-21, 49, 51, 53-55, 57-60 indefinite under 35 U.S.C. 112, second paragraph relative to the recitation of "calpain 10?"

Issues under 35 U.S.C. 112, first paragraph:

2. Do claims 19 and 53 lack written description under 35 U.S.C. 112, first paragraph for the phrase "amino acids 1-47 of SEQ ID NO:2?"

3. Do claims 18-21, 49-51, and 53-64 lack written description under 35 U.S.C. 112, first paragraph for the phrase "calpain 10?"

4. Do claims 18-21, 49-51,53-64 lack enablement under 35 U.S.C. 112, first paragraph regarding the method of screening for inhibitors of calpain 10 molecules?

B. Issues on Appeal, if the Amendment Filed Concurrently Herewith is not Entered.

If the Amendment filed concurrently herewith is entered, then the claims on appeal with be the claims set forth in Appendix A, and the six issues on appeal will be as follows:

Issues under 35 U.S.C. 112, second paragraph:

1. Are claims 18-21 and 54 indefinite under 35 U.S.C. 112, second paragraph related to the recitation of "standard activity?"

2. Are claims 18-21, 49, 51, 53-55, 57-60 indefinite under 35 U.S.C. 112, second paragraph relative to the recitation of "calpain 10?"

3. Is claim 53 indefinte under 35 U.S.C. 112, second paragraph relative to its dependency on claim 52?

Issues under 35 U.S.C. 112, first paragraph:

4. Do claims 19 and 53 lack written description under 35 U.S.C. 112, first paragraph for the phrase "amino acids 1-47 of SEQ ID NO:2?"

5. Do claims 18-21, 49-51, and 53-64 lack written description under 35 U.S.C. 112, first paragraph for the phrase "calpain 10?"

6. Do claims 18-21, 49-51, and 53-64 lack enablement under 35 U.S.C. 112, first paragraph regarding the method of screening for inhibitors of calpain 10 molecules?

VII. GROUPING OF THE CLAIMS

For purposes of this Appeal, the claims stand or fall together as follows.

Claims 18-21, 54 and 114 do not stand or fall with the other claims relative to the indefiniteness rejection under 35 U.S.C. 112, second paragraph, based on the phrase "standard activity" because these are the only claims that recite the phrase or depend on a claim that recites the phrase without the further limitation thst the standard activity profile "is determined by measuring the binding of the calpain 10 polypeptide to a substrate." Of course, if the Amendment submitted concurrently with this Appeal Brief is entered, this rejection is moot.

Claims 18-21, 49, 51, 53-55, and 57-60 do not stand or fall with the other claims relative to the indefiniteness rejection under 35 U.S.C. 112, second paragraph based upon the phrase "calpain 10" because only claims 18-21, 49, 51, 53-55, and 57-60 recite the phrase "calpain 10." Additionally, claims 19 and 53, stand or fall separately from claims 18, 20, 21, 49, 51, 54-55, and 57-60 in regard to this rejection because, even though all of the claims are definite, claims 19 and 53 have additional amino acid sequence recitations upon which additional arguments for the definiteness of the claims may be based.

Claim 53 stands alone relative to the indefiniteness rejection under 35 U.S.C. 112, second paragraph relative to its dependency on claim 52. Of course, if the Amendment submitted concurrently with this Appeal Brief is entered, this rejection is moot.

Claims 19 and 53 do not stand or fall with the other claims relative to the written description rejection under 35 U.S.C. 112, first paragraph, based on the phrase "amino acids 1-47

of SEQ ID NO:2" because only claims 19 and 53 recite the phrase "amino acids 1-47 of SEQ ID NO:2."

Claims 18-21, 49-51 and 53-64 do not stand or fall with the other claims relative to the written description rejection under 35 U.S.C. 112, first paragraph, based on the phrase "calpain 10" because only claims 18-21, 49-51 and 53-64 recite the phrase "calpain 10." Additionally, claims 19 and 53, stand or fall separately from claims 18, 20, 21, 49, 51, 54-55, and 57-60 in regard to this rejection because, even though all of the claims are have written description in the specification, claims 19 and 53 have additional amino acid sequence recitations upon which additional arguments for the patentability of the claims may be based.

Claims 18-21, 49-51, and 53-64 do not stand or fall with the other claims relative to the lack of enablement rejection under 35 U.S.C. 112, first paragraph based on reference to screening for inhibitors of calpain 10 or amino acids 1-47 of SEQ ID NO:2 because only claims 18-21, 49-51 and 53-64 refer to screening for inhibitors of calpain 10 or amino acids 1-47 of SEQ ID NO:2. Additionally, claims 19 and 53, stand or fall separately from claims 18, 20, 21, 49, 51, 54-55, and 57-60 in regard to this rejection because, even though all of the claims are enabled, claims 19 and 53 have additional amino acid sequence recitations upon which additional arguments for the definiteness of the claims may be based.

VIII. SUMMARY OF THE ARGUMENT

The appealed claims are not rendered indefinite under 35 U.S.C. 112, second paragraph nor do the appealed claims lack written description or enablement under 35 U.S.C. 112, first paragraph relative to the respective rejections.

Claims 18-21 and 54 are definite under 35 U.S.C. 112, second paragraph, relative to the recitation of "standard activity." If the Amendment submitted herewith is entered, this rejection is moot. The specification and the claims read as a whole particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

Claims 18-21, 49, 51, 53-55, and 57-60 are definite under 35 U.S.C. 112, second paragraph relative to the recitation of "calpain 10." The specification and the claims read as a whole particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

Claim 53, as amended in the amendment after final filed concurrently herewith, is definite under 35 U.S.C. 112, second paragraph relative to its dependency on claim 51.

Claims 19 and 53 satisfy the written description requirement under 35 U.S.C. 112, first paragraph. Written description for the phrase "amino acids 1-47 of SEQ ID NO:2" is found in the specification at page 29 line 24. The phrase "amino acids 1-47 of SEQ ID NO:2" does not introduce new matter.

Claims 18-21, 49-51 and 53-64 satisfy the written description requirement under 35 U.S.C. 112, first paragraph. The phrase "calpain 10," is described in the specification in such a way as to reasonably convey to one of ordinary skill in the art that the inventor had possession of the claimed invention.

Claims 18-21, 49-51,53-64 satisfy the enablement requirement under 35 U.S.C. 112, first paragraph. The method of screening for inhibitors of calpain 10 molecules is described in the

specification and enables one of ordinary skill in the art to make and/or use the invention commensurate in scope with these claims.

In summary, the Examiner has not presented substantial evidence to support its position on appeal that these terms render the claims indefinite or that the specification as filed lacks written description or enablement for the pending claims.

In contrast, Appellants present overwhelming evidence in the form of citations to particular passages in the specification and to dictionary definitions that these terms do not render the present claims indefinite. Furthermore, Appellants present similar evidence regarding the written description and enablement of the pending claims. As such, the presently appealed claims are patentable.

IX. ARGUMENT

A. Substantial Evidence Required to Support the Examiner's Position on Appeal

As an initial matter, Appellants note that findings of fact and conclusions of law by the U.S. Patent and Trademark Office must be made in accordance with the Administrative Procedure Act ("APA"), 5 U.S.C. § 706(A), (E), 1994; *see also Dickinson v. Zurko*, 527 U.S. 150, 158 (1999). The Federal Circuit has held that findings of fact by the Board of Patent Appeals and Interferences must be supported by "substantial evidence" within the record pursuant to the APA. *See In re Gartside*, 203 F.3d 1305, 1314-15 (Fed. Cir. 2000). In *In re Gartside*, the Federal Circuit stated that "the 'substantial evidence' standard asks whether a reasonable fact finder could have arrived at the agency's decision." *Id.* at 1312. Thus, an

Examiner's position on Appeal must be supported by "substantial evidence" within the record in order to be upheld by the Board of Patent Appeals and Interferences.

As explained in the following arguments, the Examiner has not put forth "substantial evidence" that the presently appealed claims are indefinite. In contrast, Appellants have provided strong evidence in the form of citations to definition of the terms in the specification that the appealed claims are definite.

B. Claim Rejections Under 35 U.S.C. §112, Second Paragraph

1. Claims 18-21 and 54 are definite

The Examiner contends that claims 18-21 and 54 are indefinite in the recitation of "standard activity profile" as it is unclear, absent a statement defining the term. Appellants traverse this rejection and in the case that the concurrently filed amendment after final is not entered set forth the following arguments.

Claims 18-21 and 54 are definite. A claim is only indefinite if one of ordinary skill in the art would not understand what is claimed in light of the specification. Also, the claims read in their totality further demonstrate the clear and definite meaning of "standard activity profile." For example, claim 18 reads:

> A method of screening for a modulator of calpain 10 function comprising:
> a) obtaining a calpain 10 polypeptide;
> b) determining a standard activity profile of the calpain 10 polypeptide;
> c) contacting the calpain 10 polypeptide with a putative modulator; and
> d) assaying for a change in the standard activity profile.

It is evident from the claim read in light of the specification that a standard activity profile is the measurement of the activity of the calpain 10 polypeptide in the absence of a modulator for

purposes of comparison to the activity of the calpain 10 polypeptide in the presence of a modulator. As stated in Webster's Dictionary the definition of standard is "something established for use as a rule or basis of comparison in measuring or judging capacity, quantity, content, extent, value, quality , *etc.*," see appendix C for excerpt from Webster's. Thus, one of ordinary skill in the art would readily understand this claim. Furthermore, the specification at page 7, lines 17-19, clearly provides an example of determining a standard activity profile by measurement of calpain 10 binding to a substrate, such as synthetic Suc-Leu-Tyr-AMC.

In addition, claim 57, which recites "The method of claim 55, wherein assaying for modulation of calpain function comprises assaying for a change in the standard activity profile," further limits claim 54. Thus, the claims as written clearly define the term "standard activity profile."

2. Claims 18-21, 49, 51, 53-55 and 57-60 are definite

The Examiner contends that claims 18-21, 49, 51, 53-55 and 57-60 are indefinite in the recitation of "calpain 10" as it is unclear as to what characteristics are unique to a polypeptide having calpain 10 function. Appellants traverse this rejection.

Claims 18-21 and 54 are definite. A claim is only indefinite if one of ordinary skill in the art would not understand what is claimed in light of the specification. As stated on page 29 line 18 of the specification "Calpain 10 is a Novel Calpain-like Protease." One of ordinary skill in the art would understand the term calpain 10, particularly in light of the specification at least on pages 5 to 8; page 18; pages 29 to 32; pages 37 to 38; pages 87 to 94; FIGs 1 and 5; and the sequence listing, which provides the sequences of various isoforms of calpain 10. In fact, the sequence listing provides exemplary amino acid sequence of calpain 10. In particular, FIG. 1 describes, in detail, the exonic as well as domain structure of calpain 10. Furthermore, given the

description of methods used to identify the mouse homolog of calpain 10 one would readily be able to identify homologs of the gene by sequence and structural comparisons such as those provided in the present application. One of skill in the art would be able to differentiate and/or identify a calpain 10 sequence from a calpain 5 or a calpain 6 sequence by any of a variety of sequence analysis method available in the art. The Examiner provides no evidence to the contrary. One of ordinary skill in the art, in light of the specification, would readily differentiate calpain 10 from other calpains. The breadth of a claim should not be equated with indefiniteness.

3. Claim 53 is definite upon entry of Amendment after final

Claim 53 is rejected under 35 U.S.C. 112, second paragraph as being indefinite due to its dependency on claim 52. The Amendment filed concurrently has amended claim 53 to depend from claim 51. If the Amendment is entered this rejection will be moot. If this Amendment is not entered, Appellants will be happy to resolve this typographical error before the Examiner upon the completion of this appeal.

C. Claim Rejections Under 35 U.S.C. 112, First Paragraph

Claims 18-21, 49-51 and 53-64 are rejected under 35 U.S.C. §112, first paragraph written description requirement. Appellants traverse the rejections and cite the claims provided in Appendix A or Appendix B along with the following evidence that the Appellants were in possession of the claimed invention at the time of the filing of the present application.

To satisfy the written description requirement, possession of the invention is shown by describing all its claimed limitations, not that which is obvious (*Vas-Cath Inc. v. Mahurkar,* 19U.S.P.Q.2d 1111,1117 (Fed.Cir.1991). An applicant shows possession of the claimed

invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including . . . by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. *See, e.g., Pfaff v. Wells Electronics, Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406; *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991); MPEP 2163.

1. Claims 19 and 53 satisfy 35 U.S.C. §112, first paragraph written description requirement

Claims 19 and 53 are rejected as containing subject matter which was not described in the specification, that is the phrase "amino acids 1-47 of SEQ ID NO:2," in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The phrase "amino acids 1-47 of SEQ ID NO:2" is described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. On page 29, line 24 an exemplary coding region of exon 1 of calpain 10 is described, which is nucleotides 1375-1515. One of ordinary skill in the art would readily recognize the relationship between nucleic acid coding region and amino acid sequence, as exemplified in the specification in Table 4 on page 58. Thus, one of ordinary skill in the art would recognize that the coding region of exon 1, which is set forth in SEQ ID NO:1 and encodes the exemplary polypeptide of SEQ ID NO:2,

corresponds to the amino acids 1-47 of calpain 10. Thus, description of amino acid 1-47 of SEQ ID NO:2 can be found at least on page 29, line 24 of the specification.

2. Claims 18-21, 49-51 and 53-64 satisfy 35 U.S.C. §112, first paragraph written description requirement

Claims 18-21, 49-51 and 53-64 are rejected as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner also contends that no disclosure of the structure of other calpain polypeptides as encompassed by the claims has been provided which would allow one of skill in the art to practice the scope of the claimed method. The Examiner further contends that no disclosure of the critical structural elements of a polypeptide that have calpain activity has been provided.

Claim 18 and claim 51, from which claims 19-21, 49-50, and 52-60 depend, recite a "calpain 10 polypeptide." At page 29, lines 18-30, and pages 30-31, Appellants have provided more than adequate description of calpain 10. At these pages and in FIGs 1 and 5, as well as in an exemplary amino acid sequence set forth in SEQ ID NO:2, Appellants disclose an exemplary full length of calpain 10 and its various exon regions that are differentially spliced to create different calpain 10 isomers. Appellants also provide Table 1, at page 30 which describes the calpain 10 isoforms with indication as to the encoded exons, the polypeptide length and the sequences corresponding to the SEQ ID Nos. In FIG. 1, Appellants have diagrammed the alternative spliced forms of calpain 10 indicating the various domains. In FIG. 5, Appellants have also provided an alignment of calpain 10 and various calpains indicating the domains. On page 31, Appellants provide a structural description of the domains of calpain 10, such as the

specific calmodulin-like Ca^{2+} binding domain. In FIG. 6, Appellants have provided a phylogentic tree of the calpain large subunit. At pages 26, 148, 149, and Example 8, Appellants have provided support, as is known in the art, that calpains are a family of structurally related intracellular multidomain cysteine proteinases containing a papain-related catalytic domain, whose activity depends on calcium. Appellants have also provided in the sequence listing exemplary amino acid sequences of calpian 10 and its isoforms. Given the more than adequate description provided in the specification and figures, it would be clear to one of skill in the art that the Appellants had possession of the claimed invention at the time of filing sufficient to practice the invention.

Furthermore, the references cited and relied upon by the Examiner are irrelevant in regard to a method for screening for a modulator of calpain 10. If one was not screening with calpain 10 then one would not identify a modulator of calpain 10. The reasoning set forth by the Examiner does not address the currently claimed method. Instead the Examiner provides references to support the alteration of enzymatic activities of metabolic enzymes that are in no way related to the calpain 10 polypeptide.

For example, Bork (Genome Research, 10:398-400, 2000) is concerned with high-throughput screening and prediction of functional and structural characteristics of genes. Bork is irrelevant to a method of screening for modulators of calpain 10, there is nothing in the claim that relies on high-throughput methods or prediction of calpain 10 function.

Secondly, Van de Loo *et al.* (Proc. Natl. Acad. Sci. 92:6743-6747, 1995) is concerned with identifying a fatty acyl desaturase homolog. The percentage of homology between an oleate 12-hydroxylase, a newly cloned enzyme, and an oleate desaturase, a known enzyme, as described in Van de Loo *et al.* is irrelevant to a method of screening for a modulator of calpain

10. There is nothing in the claimed method of screening for modulators of calpain 10 that relies on the homology between oleate metabolizing enzymes.

Thirdly, Broun *et al.* (Science 282:1315-1317, 1998) address the catalytic plasticity of fatty acid modifying enzymes of plants. Broun *et al.* has no relevance to a method of screening for a modulator of a calpain 10 polypeptide. There is nothing in the claimed method of screening for modulators of calpain 10 that relies on amino acid similarity of fatty acid modifying enzymes of plants.

In addition, Seffernick *et al.* (J. Bacteriol. 183(8):2405-2410, 2001) address the identification of an adaptive alteration in a bacterial enzyme, in fact, Seffernick *et al.* state that their observations are highly exceptional, see the discussion first paragraph. The teachings of Seffernick *et al.* are not relevant to methods of screening for modulators of a calpain 10 polypeptide because of the unique evolutionary mechanisms in bacteria, see the discussion second paragraph, as well as the fact that the observation reported is attributed to a very limited number of bacterial enzymes.

Furthermore, Witkowski *et al.* (Biochemistry 38:11643-11650, 1999) address the enzymatic effects of an alteration in a β-ketoacyl synthase. The effects of amino acid modification a particular enzyme are not relevant to a method of screening for a modulator of calpain 10. The claimed method of screening for a modulator of calpain 10 does not rely on the enzymatic effects of an amino acid alteration in β-ketoacyl synthase or any other metabolic enzyme.

The references relied upon by the Examiner are irrelevant to the enablement of a method for screening for a modulator of calpain 10. The reasoning set forth by the Examiner does not address the currently claimed method. Instead the Examiner provides references to support high-

throughput screening for and alteration of enzymatic activities of metabolic enzymes. These references are in no way related to the calpain 10 protease or the methods of screening for a modulator of a calpain 10 polypeptide.

3. Claim 18-21, 49-51, and 53-64 Satisfy 35 U.S.C. §112, First Paragraph Enablement Requirement

The Examiner further contends that claims 18-21, 49-51 and 53-64 are rejected under 35 U.S.C. §112, first paragraph because the specification, while being enabling for a method of screening for inhibitors of the human calpain 10 polypeptide of SEQ ID NO: 2, does not reasonably provide enablement for a method of screening for inhibitors of any calpain 10. The Examiner further contends that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Appellants traverse the rejection and cite the claims provided in Appendix A along with the following arguments for the enablement of the claims. Appellants have provided ample teaching with respect to a calpain 10 polypeptide at least on page 29, lines 18-30 and pages 30-31. At these pages, Appellants disclose the full length of calpain 10 and its various exon regions that are differentially spliced to create different calpain 10 isomers. Table 1, on page 30 of the specification also describes the calpain 10 isoforms indicating the encoded exons, the polypeptide length, and the sequences corresponding to the SEQ ID NOs. In FIG. 1, Appellants have diagrammed the alternative spliced forms of calpain 10 indicating the various domains. In FIG. 5, Appellants have also provided an alignment of calpain 10 and various calpains indicating the domains. On page 31, Appellants provide a structural description of the domains of calpain 10, such as the specific calmodulin-like Ca^{2+} binding domain. Appellants have provided

working examples in the specification on pages 123 to pages 165 which clearly describes how to make and use the invention. Appellants have provided the sequences of calpain 10 polypeptide and its isoforms in the Sequence Listing of the application as originally filed. Appellants have provided relevant teachings to identify characteristics and functionality of calpain 10 and its isoforms, as well as the cloning and the localization of calpain 10 in the Examples of the Specification. In addition, in the Examples on pages 123-165, Appellants have provided the use of calpain 10 in detecting and analyzing polymorphisms in individuals.

The Appellants contend that the enablement requirement is met by describing any mode of enablement of the invention. Thus, the Appellants have provided evidence that makes moot the rejection of the claims as lacking enablement from the specification, figures and the sequence listing as described above.

X. CONCLUSION

In light of the foregoing, Appellants respectfully submit that the claims on appeal should not be rejected under 35 U.S.C. § 112, first paragraph or 35 U.S.C. § 112, second paragraph Reconsideration and withdrawal of the rejection is requested.

Respectfully submitted,

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Date: December 8, 2003

APPENDIX A: PENDING CLAIMS IF AMENDMENT AFTER FINAL IS ENTERED

18. A method of screening for a modulator of calpain 10 function comprising:
    a) obtaining a calpain 10 polypeptide;
    b) determining an activity profile of the calpain 10 polypeptide;
    c) contacting the calpain 10 polypeptide with a putative modulator; and
    d) assaying for a change in the activity profile.

19. The method of claim 18, wherein the calpain 10 polypeptide comprises amino acid 1 to 47 of SEQ ID NO:2.

20. The method of claim 18, wherein obtaining the calpain 10 polypeptide comprises expressing the polypeptide in a host cell.

21. The method of claim 20, wherein the calpain 10 polypeptide is isolated away from the host cell prior to contacting the calpain 10 polypeptide with the putative modulator.

49. The method of claim 19, wherein the activity profile of the calpain 10 polypeptide is determined by measuring the binding of the calpain 10 polypeptide to a synthetic substrate.

50. The method of claim 49, wherein the synthetic substrate is Suc-Leu-Tyr-amidomethylcoumarin (AMC).

51. A method of screening for a modulator of calpain 10 function comprising:
    a) obtaining an calpain 10 polypeptide;
    b) contacting the calpain 10 polypeptide with a putative modulator; and
    c) assaying for modulation of calpain 10 function by the putative modulator.

52. The method of claim 51, wherein the calpain 10 polypeptide comprises the amino acid sequence of SEQ ID NO: 2.

53. The method of claim 51, wherein the calpain 10 polypeptide has a sequence comprising amino acid 1 to 47 of SEQ ID NO:2,

54. The method of claim 51, further comprising determining an activity profile of the calpain 10 polypeptide.

55. The method of claim 54, wherein the activity profile of the calpain 10 polypeptide is determined by measuring the binding of the calpain 10 polypeptide to a synthetic substrate.

56. The method of claim 55, wherein the synthetic substrate is Suc-Leu-Tyr-amidomethylcoumarin (AMC).

57. The method of claim 55, wherein assaying for modulation of calpain 10 function comprises assaying for a change in the activity profile.

58. The method of claim 51, wherein obtaining the calpain 10 polypeptide comprises expressing the polypeptide in a host cell.

59. The method of claim 58, wherein the calpain 10 polypeptide is isolated away from the host cell prior to contacting the calpain polypeptide with the putative modulator.

60. The method of claim 51, wherein obtaining the calpain 10 polypeptide comprises obtaining a cell containing the polypeptide.

61. The method of claim 60, wherein the cell is a pancreatic cell, a muscle cell, an adipose cell, or a liver cell.

62. The method of claim 61, wherein the cell is a pancreatic cell.

63. The method of claim 62, wherein the pancreatic cell is comprised in an isolated pancreatic islet.

64. The method of claim 62, wherein the cell is a β-cell.

114. The method of claim 18, wherein the calpain 10 polypeptide comprises the amino acid sequence of SEQ ID NO:2

115. The method of claim 18, wherein the calpain 10 is a human calpain 10.

116. The method of claim 51, wherein the calpain 10 is a human calpain 10.

APPENDIX B: PENDING CLAIMS IF AMENDMENT AFTER FINAL IS NOT ENTERED

18. A method of screening for a modulator of calpain 10 function comprising:
    a) obtaining a calpain 10 polypeptide;
    b) determining a standard activity profile of the calpain 10 polypeptide;
    c) contacting the calpain 10 polypeptide with a putative modulator; and
    d) assaying for a change in the standard activity profile.

19. The method of claim 18, wherein the calpain 10 polypeptide comprises amino acid 1 to 47 of SEQ ID NO:2.

20. The method of claim 18, wherein obtaining the calpain 10 polypeptide comprises expressing the polypeptide in a host cell.

21. The method of claim 20, wherein the calpain 10 polypeptide is isolated away from the host cell prior to contacting the calpain 10 polypeptide with the putative modulator.

49. The method of claim 19, wherein the standard activity profile of the calpain 10 polypeptide is determined by measuring the binding of the calpain 10 polypeptide to a synthetic substrate.

50. The method of claim 49, wherein the synthetic substrate is Suc-Leu-Tyr-amidomethylcoumarin (AMC).

51. A method of screening for a modulator of calpain 10 function comprising:
    a) obtaining an calpain 10 polypeptide;
    b) contacting the calpain 10 polypeptide with a putative modulator; and
    c) assaying for modulation of calpain 10 function by the putative modulator.

52. The method of claim 51, wherein the calpain 10 polypeptide comprises the amino acid sequence of SEQ ID NO: 2.

53. The method of claim 52, wherein the calpain 10 polypeptide has a sequence comprising amino acid 1 to 47 of SEQ ID NO:2,

54. The method of claim 51, further comprising determining a standard activity profile of the calpain 10 polypeptide.

55. The method of claim 54, wherein the standard activity profile of the calpain 10 polypeptide is determined by measuring the binding of the calpain 10 polypeptide to a synthetic substrate.

56. The method of claim 55, wherein the synthetic substrate is Suc-Leu-Tyr-amidomethylcoumarin (AMC).

57. The method of claim 55, wherein assaying for modulation of calpain 10 function comprises assaying for a change in the standard activity profile.

58. The method of claim 51, wherein obtaining the calpain 10 polypeptide comprises expressing the polypeptide in a host cell.

59. The method of claim 58, wherein the calpain 10 polypeptide is isolated away from the host cell prior to contacting the calpain polypeptide with the putative modulator.

60. The method of claim 51, wherein obtaining the calpain 10 polypeptide comprises obtaining a cell containing the polypeptide.

61. The method of claim 60, wherein the cell is a pancreatic cell, a muscle cell, an adipose cell, or a liver cell.

62. The method of claim 61, wherein the cell is a pancreatic cell.

63. The method of claim 62, wherein the pancreatic cell is comprised in an isolated pancreatic islet.

64. The method of claim 62, wherein the cell is a β-cell.

114. The method of claim 18, wherein the calpain 10 polypeptide comprises the amino acid sequence of SEQ ID NO:2

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stand'ard, *n.* [ME.; OFr. *estandart, estendart*; prob. from Gmc. (hyp.) *standan*, to stand, and *ort*, a place; hence, a standing place.]

1. any figure or object, especially a flag or banner, used as an emblem or symbol of a people, military unit, etc.; specifically, (a) in heraldry, a long, tapering flag used as an ensign, as by a king; (b) in military usage, the color of a cavalry unit.

2. something established for use as a rule or basis of comparison in measuring or judging capacity, quantity, content, extent, value, quality, etc.; as, *standards* of weight and measure are fixed by the government.